NATIONAL VACCINE ADVISORY COMMITTEE (NVAC)
Report of the Ad Hoc Subcommittee on Childhood Vaccines
June 9, 1994

INTRODUCTION

The Public Health Service has funded two congressionally-mandated studies on the safety of childhood vaccines. The first, required by Section 312 of Public Law 99-660, entitled *Adverse Effects of Pertussis and Rubella Vaccines*, was published by the Institute of Medicine (IOM) of the National Academy of Sciences in 1991, and has resulted in recommendations for changes in the National Vaccine Injury Compensation Table, as well as proposed revisions in the Vaccine Information Materials and labeling. The second study, entitled *Adverse Events Associated with Childhood Vaccines* was mandated under Section 313 of Public Law 99-660, and published by the IOM in September 1993. An addendum to the first report, entitled *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis*, was requested by the PHS in response to a recently published long-term follow-up study of the National Childhood Encephalopathy Study, and was released by the IOM on March 2, 1994. The latter two reports were the subject of the current review (Summary Tables, Appendices C and D).

The IOM does not create policy. Rather, the IOM is able to draw upon the expertise and knowledge of noted scientists in order to interpret scientific questions. The IOM was asked by the Public Health Service to form a group to conduct an extensive review, and determine, based on the best available data that exist at the time, the strength of the causal association between the childhood vaccines other than pertussis and rubella, and a list of adverse events. In addition, the IOM Committee was encouraged to add to their review other conditions which it considered merited examination on the basis of existing information, and in several instances did so. Given the broad scope of its mandate, the Committee did not conduct original research. The IOM Committee accomplished the review through use of comprehensive literature searches, public meetings, workshops, detailed examination of case reports, both from the literature and the Vaccine Adverse Events Reporting System (VAERS) system, and presentations by scientists and other interested parties.

After preliminary review of the Section 313 report in September 1993, the Advisory Commission on Childhood Vaccines (ACCV) recommended that the

Secretary, Health and Human Services, convene a task force of appropriate experts to review the conclusions of the IOM Committee, and consider possible changes to the Vaccine Injury Compensation Table. In addition, the ACCV unanimously recommended in its March 1994 meeting that the latest IOM report on *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* be incorporated into this review.

After presentation at the National Vaccine Advisory Committee, an Ad Hoc Subcommittee of the NVAC was established, and included representatives from the Advisory Committee on Immunization Practices (ACIP), the Advisory Commission on Childhood Vaccines (ACCV), the FDA Vaccine and Related Biological Products Advisory Committee (VRBPAC), as well as the Academy of Pediatrics Committee on Infectious Diseases (Redbook) and appropriate PHS staff from the Centers for Disease Control, Vaccine Injury Compensation Program, National Vaccine Program Office, Office of the General Counsel, and Food and Drug Administration. Lastly, additional appropriate experts from the field of childhood vaccines were consulted or included. The committee and participant list for the March 15, 1994 meeting are included as Appendix A.

Table 1. Relevant Advisory Committee Responsibilities

COMMITTEE	RESPONSIBILITY	TARGET
Advisory Committee on Immunization Practices (ACIP)	Advises the CDC and the Secretary on use of vaccines	Vaccine use recommendations
Advisory Commission on Childhood Vaccines (ACCV)	Advises the Secretary on issues relating to the Vaccine Injury Compensation Program and Vaccine Information Materials (VIMs)	Vaccine Injury Table (VIT) Vaccine Information Materials (VIMs)
Vaccine and Related Biological Products Advisory Committee (VRBPAC)	Advises FDA on the regulatory responsibilities related to vaccines.	Label Package Insert
National Vaccine Advisory Committee (NVAC)	Advises the Assistant Secretary for Health on issues affecting national vaccine policy.	Ad Hoc Subcommittee Report

It is anticipated that the report of the Ad Hoc NVAC Subcommittee will facilitate the rapid review and subsequent response by the Public Health Service. It is, however, only one part of the process whereby scientific information regarding vaccines and associated adverse events is translated into national policy (Table 1).

This report will be presented to the recommending and policy bodies, specifically the ACCV, ACIP, VRBPAC, as well as the AAP Redbook and others, and their recommendations will be considered by the Secretary, Health and Human Services, in making changes to the Vaccine Injury Table, recommendations for the use of vaccines, Vaccine Information Materials and labels, as appropriate.

TASK OF THE SUBCOMMITTEE

The Ad Hoc Subcommittee was specifically asked to review the reports on *Adverse Events Associated with Childhood Vaccines* and *DPT Vaccine and Chronic Nervous System Dysfunction* and to review the findings of the IOM Committee for concurrence, non-concurrence or comment, especially if additional or new information had been considered; and to provide advice and comment on proposed changes to the Vaccine Injury Table and vaccine use recommendations for the childhood vaccines that were the subject of the IOM studies. This report will be useful to FDA in reviewing and revising vaccine labels and package inserts, as required in Section 314 of PL 99-660. In a few instances, where new data existed that had not been available for the IOM Committees to review, the Ad Hoc Subcommittee reviewed original data; otherwise, the sources for discussions were the IOM reports and findings, as well as individual expertise of committee members.

CONCLUSIONS

The extensive discussion on March 15, as well as the Subcommittee's recommendations, are summarized in Table 2. The Subcommittee concurred with the IOM report in 18 of the 22 areas specifically reviewed, and with the respective staff proposals in 20 of the 22 areas reviewed. The Subcommittee differed with either the IOM findings or the respective staff proposals, or made additional comments, in the following areas:

1. **Causal relationship of vaccine to death subsequent to a serious associated event**
2. **DT/Td/T vaccine and brachial neuritis**
3. **Measles/Mumps/Rubella vaccines and thrombocytopenia**
4. **Oral polio vaccine and Guillain-Barré syndrome**
5. **DT/Td/T vaccines and Guillain-Barré syndrome**
6. **Unconjugated Haemophilus vaccine (PRP) and early onset Hib disease**
7. **DTP vaccine and chronic encephalopathy**

DISCUSSION

1. Causal relationship of vaccine to death subsequent to a serious associated event

The IOM Committee (henceforth "the IOM") had extended the conclusion that where data supported a finding of causal relation of a vaccine to a disease or condition that had the potential to be life-threatening, that that vaccine could cause death. The Subcommittee reviewed the lack, in several instances, of any documented cases supporting this extended conclusion, and commented that in these instances, the strength of the evidence should be clearly noted **not** to be based on data. The staff proposals, which included the use of the phrase "potentially life-threatening", were considered appropriate in this context.

2. DT/Td/T vaccine and brachial neuritis

The Subcommittee concurred with the IOM conclusion that evidence favors a causal relationship between DT/Td/T vaccines and brachial neuritis (category 4). They specifically noted that all data reviewed by the IOM bearing on this association were based on adults, with the youngest possible case at age 9 years. Therefore, the Subcommittee concurred with staff proposals, with the unanimous qualifier that available data applies to adults only.

3. Measles/Mumps/Rubella (MMR) Vaccine and thrombocytopenia

The Subcommittee concurred with the IOM conclusion that in rare instances measles-containing vaccines are causally associated with thrombocytopenia, based upon biologic plausibility, case series, and uncontrolled studies (category 5). However, it did **not** concur with staff proposals in response to that determination. The discussion emphasized that the condition is benign and transient. Diagnostic criteria for consideration of thrombocytopenia are a platelet count less than $50{,}000/mm^3$, and time frame for occurrence in relation to vaccination is from 3-14 days. The Subcommittee commented that there is no evidence at this time that a history of idiopathic thrombocytopenia purpura in a child, (a condition that occurs with a known frequency in the pediatric population), is a risk modifying factor, and thus should not be a reason for exclusion of immunization.

4. Oral Polio Vaccine and Guillain-Barré syndrome

The IOM had concluded that the evidence favored the acceptance of a causal relation between oral polio vaccine (OPV) and Guillain-Barré syndrome (GBS) (category 4). The conclusion of the IOM was based on demonstrated biologic plausibility, case reports, case series, uncontrolled observational studies and two controlled observational studies. The major publication, by Kinnunen et al (1989),

was a Finnish study of an increase in the incidence of GBS following a national campaign with OPV. Ten cases of GBS occurred in OPV recipients within 10 weeks of immunization. A concern in the literature, without supporting data, is that a prior history of GBS in the 6 weeks following immunization is a potential risk-modifying factor.

The Subcommittee reviewed the original report, as well as a letter from one of the co-authors to the Centers for Disease Control which stated:

> "We felt it important to note the association, although it by no means was our intention to claim that the observation was enough to conclude that GBS is temporally associated with OPV administration. The wording in the abstract is unfortunately more conclusive than the discussion. The figure in the article describes the data in calendar quarters, but it is clearly stated in the discussion that if the blocks were constructed in another way, e.g., a time before and after starting the OPV campaign, the number of cases of GBS was similar in both blocks. Hence, the OPV campaign could not be the only explanation".

Since the publication of the IOM report in 1993, additional information had been published by Rantala et al (J. Pediatrics, 124:2, 220-223, February 1994) which was examined and discussed by the Subcommittee. This new study is a retrospective epidemiologic survey of GBS in Southern California. The study failed to show a temporal association between GBS and OPV after studying 93 cases of GBS from 22 hospitals over 6 years.

On the basis of the available information, the Subcommittee voted **unanimously** not to accept a causal association (IOM category 4 or 5). The concensus was in support of staff proposals, which were to not add this condition to the VIT, and to describe the evidence in the vaccine recommendations, but not to describe this level of detail in the shorter VIMs.

5. DT/Td/T vaccines and Guillain-Barré syndrome

The relation between tetanus-containing vaccines and GBS was defined by the IOM as category 4. This was based on case reports, with detailed discussion of a single person from Australia with a history of multiple episodes of vaccine-associated GBS, as well as non-vaccine-associated GBS. There was <u>not</u> a clear consensus of the Subcommittee on whether this relation should remain category 4, due to concerns about over-estimation of risk in the pediatric population, which generally has low rates. On a formal vote, the Subcommittee voted 6+/5- to concur with the IOM, as the single case with multiple episodes favored the acceptance of a causal relation. Both the discussion and the formal vote revealed the lack of clear concensus by the Subcommittee, reflecting resistance to interpretation of the

available data implying an increased risk in children immunized with tetanus-containing vaccines. The Subcommittee also voted (11+/0-) to concur with staff proposal not to add this condition to the VIT in light of the fact that a vaccine-related condition could be covered under the compensation program by proof of "causation in fact". Section 2111 (c)(1)(C)(ii) allows a petitioner to obtain compensation on showing that a vaccine actually caused a condition, even if it is not listed on the VIT.

6. Unconjugated Haemophilus vaccine (PRP) and post vaccination Hib disease

The relation between unconjugated Hib vaccine (specifically only PRP) and the onset of *Haemophilus influenzae* type b disease shortly after vaccination was noted as category 4 in the IOM report, on the basis of biologic plausibility, animal studies, and uncontrolled clinical studies. The Subcommittee concurred with the IOM category 4 conclusion for unconjugated PRP and Hib disease within 7 days, but did **not** concur with staff proposal as stated, and recommended that at the time Hib is added to the VIT, it be considered that this disease be added to the table specifically only for the unconjugated PRP vaccine.

The Subcommittee also concurred with the category 3 (no relation) for conjugated Hib vaccines (including PRP-D) and this disease. The Subcommittee also commented that the type of Hib vaccine that would be universally recommended, mandated, or covered by the compensation program must be specified in order to avoid confusion with the unconjugated vaccine.

7. DTP vaccine and chronic encephalopathy

The recently published IOM report entitled "DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis" was the focus of the Subcommittee deliberations. The executive summary of this report was published in the Federal Register on March 24, 1994, in order to provide public notice and an additional period for public comment on proposed regulations to amend the Vaccine Injury Table governing the National Vaccine Injury Compensation Program (NVICP) (Appendix B).

The IOM was asked to consider how the recently published information on the 10-year follow-up of the National Childhood Encephalopathy Study (NCES) (Miller et al, 1993) would affect the conclusions of the original report that considered adverse events associated with [whole cell] pertussis vaccines, whereby chronic neurologic damage was classified as category 2 (evidence insufficient to indicate a causal relation) [footnote: the Subcommittee specifically noted that the data pertained to whole cell pertussis vaccines only, and not to the newer acellular vaccines]. The IOM reached three conclusions:

First -- that the evidence is insufficient to indicate whether or not DPT increases the overall risk in children of chronic nervous system dysfunction.

Second -- that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experienced a serious acute neurologic illness within 7 days after vaccine.

Third -- that the evidence remains insufficient to indicate the presence or absence of a causal relation between DPT and chronic nervous system dysfunction under any other circumstances.

The Subcommittee recognized the limitations of the NCES follow-up data, but acknowledged it as the most comprehensive long-term study on this subject conducted to date. Overall, given the rareness of the diseases and the variability in exposures (one member emphasized that whole-cell vaccines vary from each other), it was recognized as an extremely difficult, and probably impossible, study to replicate or improve. Reservations included the lack of neuropathologic studies on the children; that even NCES authors do not claim that all DTP-temporally-associated cases are due to the vaccine, and the possibility that alternative etiologic diagnoses, such as Coxsackie meningitis, had not been clearly ruled out, as well as some confusion over the specific number of children defined as cases at different times. The range of disorders included under the umbrella of "chronic nervous dysfunction" were non-specific, and failed to describe a syndrome of vaccine-associated encephalopathy.

During the discussion, the Committee was asked to address the following questions regarding the IOM report:

a. Comment whether DTP vaccine can cause both an acute encephalopathy and residual neurologic damage (chronic encephalopathy)?

The IOM report makes a distinction that was found useful by the Subcommittee: that the relationship observed by Miller can be explained by three alternative scenarios, and one of the three would lead to the conclusion that the relation is not causal, while the other two would lead to the opposite conclusion. It is not possible to distinguish among these at this time. One Subcommittee member stated that since chronic encephalopathy is on the Vaccine Injury Table, the "burden of proof" was placed on the Subcommittee to change the table only in response to new scientific data. The Subcommittee reached consensus on the following statement:

"Children immunized with whole-cell DTP vaccines rarely experience acute, serious neurologic events that require hospitalization. An important question

pertains to the long-term complications of these events. Among all children hospitalized with serious neurologic events, irrespective of their etiology or relationship to DTP, there is a potential for the presence of neurologic dysfunction when they are evaluated 10 years later. However, the data are insufficient to accept or reject whether DTP administration prior to the acute, serious neurologic event influenced the potential for neurologic dysfunction 10 years later."

b. Comment whether the IOM report supports the conclusion that DTP vaccine can cause chronic encephalopathy in the absence of clinical signs of acute encephalopathy in the period following DTP vaccination?

The Subcommittee voted unanimously that the IOM report does not support this conclusion. It was specified that the extension of the IOM report applies solely to extremely ill children with severe acute encephalopathy.

c. Is there sufficient evidence to change the time interval following DTP vaccine from 3 to 7 days for purposes of the encephalopathy provision of the VICP?

The Subcommittee consensus was that there was **not** sufficient evidence to change the interval for compensation of encephalopathy from 3 to 7 days.

d. Is the NCES working definition of acute neurologic illness consistent with current medical understanding of encephalopathy that can be caused by DTP vaccine?

The Subcommittee emphasized, as did the IOM report, that there is not a distinctive neuropathologic syndrome related to DTP vaccination; rather, it is a theoretical construct. The medical literature related to acute encephalopathy includes febrile seizures. The Subcommittee recognized that the NCES criteria for inclusion into the study cast a very broad net, but that many children who were cases within NCES had been hospitalized with very severe acute disease. There was consensus that the NCES definition of acute neurologic illness was **not** consistent with current medical understanding of "acute encephalopathy" as an acute, generalized disorder of the brain.

ADDITIONAL COMMENTS

Overall, the Subcommittee recognized that categorization of the data relating to causality as was done by the IOM Committee should not be directly implemented as policy, but should be considered on a case-by-case basis. Similarly the Subcommittee reviewed the category 2 conditions ("Evidence is inadequate to accept or reject a causal relation") and unanimously voted to recommend that

these should not be covered under the VIT. The Subcommittee noted that residual seizure disorder following MMR vaccine is a condition that is currently on the VIT, which is inconsistent with the determination of the IOM that it is a category 2 condition, and added that residual seizure disorder must follow an acute encephalopathy for any vaccine.

APPENDICES

A. Membership of committee and participants
B. Federal Register Notice - March 24, 1994
C. IOM Summary Table 1.2 (1991)
D. IOM Summary Table 1.2 (1993)

SUMMARY

Report of the NVAC Ad Hoc Subcommittee on Childhood Vaccines

Table 2. Summary (IOM categories 3, 4 and 5)

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
DT/Td/ T	Cat 5 -- Anaphylaxis	Case reports	Current: Listed on VIT Proposed: No change	Current: No Proposed: Add statement that condition is associated and can be life threatening	Condition included in Adverse Reactions (AR) section, wording differs	A) Concur with IOM conclusion B) Concur with staff proposal
	Cat unspecified -- Death from Anaphylaxis	Based on animal model and two case reports	Current: Death as a sequalae of a listed condition is itself covered by the VIT Proposed: No change	Current: No Proposed: Add statement that condition is associated and can be life threatening	Not presently included - Proposed: Add to label.	A) Concur with IOM conclusion B) Concur with staff proposal

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
DT/Td/ T	Cat 4 -- Guillan-Barre Syndrome	Case reports, single case with multiple events who has also had non-vaccine associated GBS	Current: Not listed on VIT Proposed: No Change (would be covered under "causation-in-fact")	Current: No Proposed: Add case report and RMF, in context of rareness of association	Some (not all) include in AR section	A) Concur with IOM conclusion (6+/5-) Comment: Single case establishes causation, but does not imply increased risk in the population B) Concur with staff proposal.
DT/Td/ T	Cat 4-- Brachial neuritis	Case reports and uncontrolled observational studies RR=5-10, excess risk is 0.5-1/100,000 vaccine recipients	Current: Not listed on VIT Proposed: Add to VIT, time frame of 4-21 days post vaccination. Diagnostic criteria?	Current: No Proposed: Add that it has been observed in adult vaccinees (RR 5-10)	Include "brachial plexus neuropathies" in AR section	A) Concur with IOM conclusion B) Concur with staff proposal, with unanimous qualifier that available data applies to adults only; no cases recorded in children

VIT=Vaccine Injury Table; RR=relative risk; RMF=Risk modifying factor; Cat= IOM categorical classification; ACIP recs=ACIP recommendations for use of vaccine; AR=Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
DT/Td/ T	Cat 3 -- Encephalopathy	Biologic evidence, case reports and controlled obs. studies	Listed on VIT Propose removing	Current: Not mentioned Proposed: No change	Included in some	A) Concur with IOM conclusion B) NA
	Cat 3 -- Infantile Spasms	Uncontrolled obs. studies and NCES analysis	Not on VIT. No change proposed	Current: Not mentioned Proposed: No change	Not included any	A) Concur with IOM conclusion B) NA
	Cat 3 -- Death from SIDS	Uncontrolled obs. studies	Not on VIT No change proposed	Current: Not mentioned Proposed: No change	Included in some	A) Concur with IOM conclusion B) NA

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
Measles (MMR)	Cat 5 -- Thrombocytopenia	Biologic plausibility, case series, and uncontrolled studies I = 1/30,000-40,000 doses Potential RMF = hx of ITP	Current: Not listed on VIT Proposed: Consider for change ?Diagnostic criteria ?Timeframe	Current: No Proposed: Include, cite incidence from studies, and comment on benign clinical course; Previous ITP or low platelet count may be at increased risk; follow carefully	Included in AR	A) Concur with IOM conclusion B) Did NOT CONCUR with staff proposal to add to VIT. Comments: Emphasis that condition generally benign and transient, and mechanism unknown. Diagnostic criteria at least < 50,000, and timeframe for occurrence 3-14 days appropriate. History of ITP not a clear risk modifying factor.
	Category unspecified. Death from thrombocytopenia	Based on potential for death following thrombocytopenia	Current: Not listed on VIT Proposed: Death as a sequalae of a condition added to the VIT is itself covered by the VIT	Current: No Proposed: Include that this AE can be potentially life threatening, although no deaths reported	Does not include death	A) Not proven -- remain theoretical. B) Did not concur with staff proposal (as above) re: VIT. Support approach to recommendations.

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
Measles (MMR only)	Cat 5 -- Anaphylaxis	Case reports, case series, uncontrolled studies; Incidence = 1/20,000--1/Million doses; RMF = Hx allergy to egg and neomycin	Current: Listed on VIT Proposed: No change	Current: Yes, in individual and combined Proposed change: none	Included	A) Concur with IOM conclusion B) Concur with staff proposal
	Category unstated-Death from anaphylaxis	No case reports; no direct evidence	Current: Covered under VIT - Death as a sequalae of a listed condition is itself covered by the VIT Proposed: No change	Current: No Proposed: add "events are potentially life-threatening"	Death not included. Proposed to add to label.	A) Concur with IOM conclusion B) Concur with staff proposal

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
Measles	Cat 5 -- Death from measles-vaccine associated infection	Case reports of deaths in immuno-compromised children	Current: Covered under VICP by proof of "Causation in fact" [section 2111 (c)(1) (C)(ii)] Proposed: No change	Current: No Proposed: Although rare, evidence has linked measles vax to death in some severely immunocompromised children	No	A) Concur with IOM conclusion B) Concur with staff proposal
Measles (mono-valent)	Cat 4 -- Anaphylaxis	Data less convincing than MMR	Current: Listed on VIT Proposed: No change	Current: No Proposed: Include	Included	A) Concur with IOM conclusion B) Concur with staff proposal
	Category unstated-Death from anaphylaxis	On potential for condition to be fatal; no case reports	Current: Covered by VIT. Proposed: No change.	Proposed: "These conditions can be life-threatening"	Not included. Proposed to add to label.	A) Concur with IOM conclusion B) Concur with staff proposal

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
OPV	Cat 5 -- Poliomyelitis	Biologic plausibility, case series, uncontrolled obs. studies RMF = immuno-deficiency due to congenital syndromes, ? HIV	Current: Listed on VIT Proposed: No change	Current: Yes	Included	A) Concur with IOM conclusion B) Concur with staff proposal
OPV	Cat 5 -- Death from polio vaccine associated infection	Case reports, primarily immuno-compromised	Current: Covered under the VICP by proof of "Causation in Fact" Section 2111(c)(i)(C)(ii) Proposed: No change	Current: Death not mentioned Proposed: Associated with paralytic polio, and very rarely, death in immunocomp	No	A) Concur with IOM conclusion B) Concur with staff proposal

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
OPV	Cat 4 - Guillan-Barré Syndrome	Biologic plausibility, case reports, series, and controlled studies Incidence: RR in Finland 3.5; excess risk in children 0.1/100,000 RMF: ? GBS in past 6 weeks	Current: Not listed on VIT Proposed: No change	Current: No Proposed: Ecologic study in Finland but followed by reanalysis of Finnish data and new U.S. data provide evidence against. Would also be reflected in VIMs.	Included	A) Non-concur with IOM conclusions. B) Concur with staff proposal.
HBV	Cat 5 - Anaphylaxis	Biologic plausibility and VAERS case reports	Current: Vaccine not on VIT Proposed: List condition on VIT when vaccine added to program	Current: No Proposed: Evidence supports, number of cases	Included	A) Concur with IOM conclusion B) Concur with staff proposal. Committee noted that addition of vaccine to table will permit filing for cases up to 8 years prior to new regulation.

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
HBV	Category unstated- Death from anaphylaxis	Based on potential for causing deaths - no case reports	Current: Vaccine not on VIT Proposed: Since condition proposed for inclusion, would be covered by VIT	Current: No Proposed: Add that condition can be fatal	Not included. Under review.	A) Concur with IOM conclusion B) Concur with staff proposal
Hib (PRP only - not PRP conju-gate)	Cat 4 - Early onset Hib disease	Biologic plausibility, uncontrolled trials	*Current: Vaccine not on VIT Proposed: Do not list on VIT when vaccine added to program	No active recommendation, not in distribution.	PRP is no longer in distribution.	A) Concur with IOM conclusion B) Did **not** concur with staff proposal to not list unconjugated. Committee recommended to specificy type of vaccine that is universally recommended or mandated to avoid confusion
Hib	Cat 3 - Early onset Hib/ conjugates	Prospective obs. studies	*Current: Vaccine not on VIT Proposed: Will not add condition when vaccine added	Not included	Included in some	A) Concur with IOM conclusion B) Concur with staff proposal

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

Vaccine	IOM Category -- Disease	Basis for Conclusion	VIT Table	ACIP Recs	Current Label/package insert**	NVAC SubCommittee Recommendations
DTP Whole-cell vaccine only	"Chronic nervous system dysfunction" Cat 2: Overall Cat 4: NCES criteria for encephalopathy.	NCES follow-up study Excess risk: 0-10.5 per million immunizations RMFs: None known	Address questions below	Current: Propose: Discussed, Evaluation of whether addressed adequately pending	Not included	A) See text.

During the discussion, the Committee was asked to address the following questions regarding the 1994 IOM report on the Miller 10-year follow-up of the NCES:

1. Comment whether DTP vaccine can cause both an acute encephalopathy and residual neurologic damage (chronic encephalopathy)?

2. Comment whether the IOM report supports the conclusion that DTP vaccine can cause chronic encephalopathy in the absence of clinical signs of acute encephalopathy in the period following DTP vaccination?

3. Is there sufficient evidence to change the time interval following DTP vaccine from 3 to 7 days for purposes of the encephalopathy provision of the VICP?

4. Is the NCES working definition of acute neurologic illness consistent with current medical understanding of encephalopathy that can be caused by DTP vaccine?

VIT = Vaccine Injury Table; RR = relative risk; RMF = Risk modifying factor; Cat = IOM categorical classification; ACIP recs = ACIP recommendations for use of vaccine; AR = Adverse Reactions section of package insert; *Vaccine not currently on VIT; **FDA is conducting review and revision of vaccine labels/package inserts under Section 312; this report will be considered at that time

NATIONAL VACCINE ADVISORY COMMITTEE
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Karen Chaitkin, FDA
John La Montagne, NIAID

proposes to rename 40 CFR 85.1706 "Manufacturer-owned exemption". For purposes of this provision, this substitution does not expand the meaning of the subject terms, but only distinguishes them from the exemptions ded to ICIs under Subpart P in to eliminate possible confusion created by the current use of the terms.

C. Display Exemption

EPA is also proposing a revision to the display exemption found at 40 CFR 85.1511(b)(4) and 85.1707. Presently, EPA will grant a temporary display exemption for uncertified motor vehicles under certain conditions. Although the exemption will be retained, EPA is proposing several clarifications. These clarifications include incorporating EPA's policy of granting the display exemption for business or public display purposes only; and establishing a time limit for the display exemption. In addition, the language in the display exemption in 40 CFR 85.1511(b)(4) and 40 CFR 85.1707 will be reconciled so that both provisions will prohibit use on public streets and highways except for purposes incident and necessary to the display purpose.

IV. Administrative Requirements

A. Administrative Designation and Regulatory Analysis Executive Order 12866

Under Executive Order 12866, [58 FR 5 (October 4, 1993)] the Agency determine whether the regulatory action is "significant" and therefore subject to OMB review and the requirements of the Executive Order. The Order defines "significant regulatory action" as one that is likely to result in a rule that may:

(1) Have an annual effect on the economy of $100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local or tribal governments or communities;

(2) Create a serious inconsistency or otherwise interfere with an action taken or planned by another agency;

(3) Materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or

(4) Raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the Executive Order.

It has been determined that this rule is not a "significant regulatory action" under the terms of Executive Order 12866 and is therefore not subject to OMB review.

B. Paperwork Reduction Act

The information collection requirements in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB) under the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.* An Information Collection Request document has been prepared by EPA (OMB control number 2060–0095, ICR No. 10.06) and a copy may be obtained from Sandy Farmer, Information Policy Branch,; EPA; 401 M St., SW. (Mail Code 2136); Washington, DC 20460 or by calling (202) 260–2740.

This collection of information has an estimated reporting burden averaging 0.5 hours per response and an estimated annual recordkeeping burden averaging 0.3 hours per respondent. These estimates include time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding the burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Chief, Information Policy Branch; EPA; 401 M St., SW. (Mail Code 2136); Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503, marked "Attention: Desk Officer for EPA." The final Rule will respond to any OMB or public comments on the information collection requirements contained in this proposal.

C. Impact on Small Entities

The Regulatory Flexibility Act of 1980 requires federal agencies to identify potentially adverse impacts of federal regulations upon small entities. In instances where significant impacts are possible on a substantial number of these entities, agencies are required to perform a Regulatory Flexibility Analysis.

There will not be a significant impact on a substantial number of small business entities because the proposed rule benefits the small businesses that import nonconforming vehicles into the United States, allowing them additional options for importing these vehicles and minimizing their costs.

Therefore, as required under section 605 of the Regulatory Flexibility Act, 5 U.S.C. 601 *et. seq.*, the Administrator certifies that this regulation does not have a significant impact on a substantial number of small entities.

D. Statutory Authority

Subpart P—Secs. 203, 206, 207, 208, 301 and 307, Clean Air Act, as amended (42 U.S.C. 7522, 7525, 7541, 7542, 7601 and 7607).

Subpart R—Secs. 203(b)(1), 216(2), 301 and 307, Clean Air Act, as amended (42 U.S.C. 7522(b)(1), 7550(2), 7601 and 7607).

List of Subjects

40 CFR Part 85

Imports labeling, Motor vehicle pollution, Reporting and recordkeeping requirements, Research, Warranties.

40 CFR Part 600

Electric power, Energy conservation, Gasoline, Labeling, Administrative practice and procedure, Fuel economy.

Dated: March 17, 1994.

Carol M. Browner,

Administrator.

[FR Doc. 94–6949 Filed 3–23–94, 8:45 am]

BILLING CODE 6560–50–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

42 CFR Part 100

National Vaccine Injury Compensation Program: Revision to Vaccine Injury Table

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice of Extension of Public Comment Period.

SUMMARY: This document affords interested members of the public an additional 30 days to comment on proposed regulations to amend the Vaccine Injury Table governing the National Vaccine Injury Compensation Program (VICP) due to recent publication of a study that may be relevant to the vaccine injury table.

DATES: Comments must be submitted on or before April 25, 1994.

ADDRESSES: Written comments should be addressed to Fitzhugh Mullan, M.D., Director, Bureau of Health Professions (BHPr), Health Resources and Services Administration (HRSA), room 8–05, Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857. All comments received will be available for public inspection and copying at the Office of Program Development, BHPr, room 8A–55, Parklawn Building, at the above address weekdays (Federal holidays excepted) between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: Geoffrey Evans, M.D., Deputy Director,

Division of Vaccine Injury Compensation, BHPr, (301) 443–6593. David Benor, Senior Attorney, Office of the General Counsel, (301) 443–2006.

SUPPLEMENTARY INFORMATION: The Agency is publishing this Notice to afford members of the public an additional 30 days to provide comments on proposed regulations to amend the Vaccine Injury Table governing the National Vaccine Injury Compensation Program (hereinafter "VICP" or "Program"). The VICP was established by the National Childhood Vaccine Injury Act of 1986, Pub. L. 99–660 [42 U.S.C. 300aa–10 et seq.] (Act), and provides a system of no-fault compensation for certain individuals who have been injured by specific childhood vaccines. Petitions for compensation under this Program are filed with the United States Court of Federal Claims, with a copy served on the Secretary, who is denominated the "Respondent." The Vaccine Injury Table (Table) included in the Act establishes presumptions about causation of certain illnesses and conditions, which are used by the U.S. Court of Federal Claims to adjudicate petitions.

Under section 312 of the Act, Congress mandated that the Secretary review the scientific literature and other information on specific adverse consequences of pertussis and rubella vaccines. In accordance with the requirements of that law, the Secretary entered into a contract with the Institute of Medicine (IOM) to perform this review. The IOM published on August 27, 1991 a report of its review entitled, "Adverse Effects of Pertussis and Rubella Vaccines" (hereinafter "IOM Report.")

Section 312 also required the Secretary to propose regulations to amend the Table as a result of such findings. Accordingly, on August 14, 1992, the Assistant Secretary for Health, with the approval of the Secretary of Health and Human Services (the Secretary) published in the Federal Register (57 FR 36878) a Notice of Proposed Rulemaking (NPRM) to amend the Table. The NPRM was issued pursuant to section 2114 of the Act, which authorizes the Secretary to promulgate regulations to modify the Table. As required by section 2114(c) of the Act, the Department provided for a 6-month comment period which closed on February 11, 1993. In addition, on December 3, 1992, the Department held a public hearing for the purpose of receiving oral testimony on the proposed rule.

The Agency analyzed the comments received in preparation for publication of the final rule. During this process, however, the Agency became aware of the imminent publication of a 10-year follow-up study to the National Childhood Encephalopathy Study (Madge N., Diamond J., Miller D., Ross E., McManus C., Wadsworth J., Yule W. The National Childhood Encephalopathy Study: A 10-year follow-up. A report of the medical, social, behavioural and educational outcomes after serious, acute, neurologic illness in early childhood. Developmental Medicine and Child Neurology 1993; Supplement No. 68;35(7):1–118; Miller D.L., Madge N., Diamond J., Wadsworth J., Ross E. Pertussis immunization and serious acute neurological illness in children. British medical Journal 1993; 307:1171–1176, hereinafter "Miller study."). Because the National Childhood Encephalopathy Study (NCES) was reviewed initially by the IOM, and because the Miller study looked specifically at the relationship between vaccine administration and resulting neurological damage, the Department determined that it should not proceed with publication of the final rule until there had been a sufficient opportunity to consider the conclusions of the new Miller study. Accordingly, the Department asked the IOM to convene a Committee for purposes of evaluating the Miller study in light of the conclusions of its initial report. On March 2, 1994, the Institute of Medicine issued a report entitled "DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis."

The Agency has determined that the public should have an additional 30 days to comment on the conclusions of this report prior to publication of the final rule. Only those comments addressing the conclusions of this latest IOM report will be considered. Commenters should address whether the proposed rule should be modified in light of the conclusions of this latest IOM report. The Department will consider carefully all comments received, and will address these comments in the preamble to the final rule.

The Department is not able to reproduce herein the entire study for review by the public. Set forth below, however, is the Executive Summary of the report containing the IOM's conclusions. Copies of the full report can be obtained by contacting the National Academy of Sciences, 2101 Constitution Avenue, NW., Washington, DC 20077–5576.

Executive Summary

An Institute of Medicine (IOM) committee recently concluded that the evidence is consistent with a causal relation between vaccination with DPT and acute encephalopathy (IOM, 1991), and the excess risk was estimated to range from 0 to 10.5 per million DPT immunizations. However, the same IOM committee also concluded that the evidence was insufficient to indicate a causal relation between DPT and permanent neurologic damage (IOM, 1991). In fact, the relation between DPT and chronic nervous system dysfunction had not been studied in a rigorous scientific manner until recently. Because the evidence has been so limited, the appearance of a single new report, a 10-year follow-up to the National Childhood Encephalopathy Study (NCES, Miller et al., 1993), prompted the U.S. Public Health Service to ask IOM to convene the Committee to Study New Research on Vaccines with the charge of studying the new data and, if warranted, reevaluating the causal relation between DPT and chronic nervous system dysfunction.

The NCES reported that the occurrence of hospitalization for serious neurologic disorders among 2- to 35-month-old children is very strongly related to the occurrence of death or nervous system dysfunction (neurologic, behavioral, educational, motor, sensory, or self-care impairment) up to 10 years (Madge et al., 1993, Miller et al. 1993). Children who experienced the rare but serious acute neurologic disorder within 7 days after receiving DPT were no more or less likely to experience documented chronic nervous system dysfunction or to have died within 10 years of the acute disorder than children who had not received DPT within 7 days prior to the onset of the disorder. There were no special characteristics associated with the acute or chronic nervous system illnesses linked to DPT exposure.

The NCES did not investigate the possibility of a direct relation between DPT and chronic nervous system dysfunction, that is, in the absence of a serious acute neurologic illness that occurs within 7 days after receiving DPT. The NCES provides data only on the limited case of a possible relation between DPT and chronic nervous system dysfunction in those children in whom a serious acute neurologic illness followed DPT vaccination within 7 days.

The committee posits three possible scenarios whereby the acute neurologic illnesses that follow DPT might be related to chronic nervous system dysfunction.

1. DPT administration might cause serious acute neurologic illness and subsequent chronic dysfunction in children who might not have otherwise experienced either an acute neurologic illness or chronic dysfunction in the absence of DPT.

2. DPT might trigger (and thereby be an immediate or proximate cause) an acute neurologic illness and subsequent chronic dysfunction in children with underlying brain or metabolic abnormalities. Such children might experience acute neurologic illness and subsequent chronic dysfunction in association with some trigger other than DPT.

3. DPT might cause an acute neurologic illness in children with underlying brain or metabolic abnormalities that would themselves eventually have led to chronic dysfunction even in the absence of an acute neurologic illness.

The Committee believes its conclusions take into account the fact that the data do not support any one of these scenarios over the others. Because the NCES did not (and probably could not) rule out the possibility that only children with underlying brain or metabolic abnormalities react to stimuli such as DPT with acute neurologic illness, and no other studies establish or rule out such a possibility, the committee concludes that the evidence is insufficient to indicate whether or not DPT increases the overall risk in children of chronic nervous system dysfunction.

The NCES data are consistent with the possibility that some children without underlying brain or metabolic abnormalities might experience serious, acute neurologic illness within 7 days after receiving DPT and that acute neurologic illness will have chronic nervous system sequelae. The NCES data also are consistent with the possibility that some children with underlying brain or metabolic abnormalities (which foster a "triggering" by DPT of an acute neurologic illness) might go on to develop chronic nervous system dysfunction due to a DPT-triggered acute illness. Therefore, the committee concludes that the balance of evidence is consistent with a causal relation between DPT and the forms of chronic nervous system dysfunction described in the NCES in those children who experience a serious, acute neurologic illness within 7 days after receiving DPT vaccine. This serious, acute neurologic response to DPT is a rare event. The excess risk has been estimated to range from 0 to 10.5 per million immunizations (IOM, 1991). The evidence does not "establish" or "prove" a causal relation. The evidence remains insufficient to indicate the presence or absence of a causal relation between DPT and chronic nervous system dysfunction under any other circumstances. That is, because the NCES is the only systematic study of long-term dysfunctions after DPT, the committee can only comment on the causal relation between DPT and those long-term dysfunctions under the conditions studied by the NCES. In particular, it should be noted that the long term dysfunctions associated with DPT followed a serious acute neurologic illness that occurred in children within 7 days after receiving DPT.

Dated: March 18, 1994.

Ciro V. Sumaya,

Administrator.

[FR Doc. 94-6856 Filed 3-23-94; 8:45 am]

BILLING CODE 4160-01-P

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 73

[MM Docket No. 94-21; RM-8427]

Radio Broadcasting Services; Garapan, Saipan, Northern Mariana Islands

AGENCY: Federal Communications Commission.

ACTION: Proposed rule

SUMMARY: The Commission requests comments on a petition filed by Inter-Island Communications, Inc., proposing the allotment of Channel 266C at Garapan, Saipan, Northern Mariana Islands, as the community's fifth local FM transmission service. Channel 266C can be allotted to Garapan in compliance with the Commission's minimum distance separation requirements without the imposition of a site restriction at petitioner's requested site. The coordinates for Channel 266C at Garapan are North Latitude 15-12-26, and East Longitude 145-42-57.

DATES: Comments must be filed on or before May 12, 1994 and reply comments on or before May 27, 1994.

ADDRESSES: Federal Communications Commission, Washington, DC 20554. In addition to filing comments with the FCC, interested parties should serve the petitioner, or its counsel or consultant, as follows: Peter Gutmann, Esq., Pepper & Corazzini, 1776 K Street NW., suite 200, Washington, DC 20006 (Counsel for Petitioner).

FOR FURTHER INFORMATION CONTACT: Sharon P. McDonald, Mass Media Bureau, (202) 634-6530.

SUPPLEMENTARY INFORMATION: This is a synopsis of the Commission's Notice of Proposed Rule Making, MM Docket No. 94-21, adopted March 9, 1994, and released March 21, 1994. The full text of this Commission decision is available for inspection and copying during normal business hours in the FCC Reference Center (room 239), 1919 M Street NW., Washington, DC. The complete text of this decision may also be purchased from the Commission's copy contractor, International Transcription Service, Inc., (202) 857-3800, 2100 M Street NW., suite 140, Washington, DC 20037.

Provisions of the Regulatory Flexibility Act of 1980 do not apply to this proceeding.

Members of the public should note that from the time a Notice of Proposed Rule Making is issued until the matter is no longer subject to Commission consideration or court review, all *ex parte* contacts are prohibited in Commission proceedings, such as this one, which involve channel allotments. See 47 CFR 1.1204(b) for rules governing permissible *ex parte* contacts.

For information regarding proper filing procedures for comments, see 47 CFR 1.415 and 1.420.

List of Subjects in 47 CFR Part 73

Radio broadcasting.

Federal Communications Commission.

Victoria M. McCauley,

Acting Chief, Allocations Branch, Policy and Rules Division, Mass Media Bureau.

[FR Doc. 94-6913 Filed 3-23-94; 8:45 am]

BILLING CODE 6712-01-M

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47 CFR Part 73

[MM Docket No. 94-23, RM-8439]

Radio Broadcasting Services; Mabton, WA

AGENCY: Federal Communications Commission.

ACTION: Proposed rule.

SUMMARY: The Commission requests comments on a petition filed by First Love Ministries, Inc., proposing the allotment of Channel 254A at Mabton, Washington, as the community's first local aural transmission service. Channel 254A can be allotted to Mabton in compliance with the minimum Commission's minimum distance separation requirements without the imposition of a site restriction. The coordinates for Channel 254A at Mabton are North Latitude 46-12-42 and West

'LE 1-2 Conclusions Based on the Evidence Bearing on Causality

Diffd/T	Measles[a]	Mumps[a]	OPV/IPV[b]	Hepatitis B	*H. influenzae* type b
Category 1: No Evidence Bearing on a Causal Relation					
		Neuropathy	Transverse myelitis (IPV)		
		Residual seizure disorder	Thrombocytopenia (IPV)		
			Anaphylaxis (IPV)		
Category 2: The Evidence Is Inadequate to Accept or Reject a Causal Relation					
Residual seizure disorder other than infantile spasms	Encephalopathy	Encephalopathy	Transverse myelitis (OPV)	Guillain-Barré syndrome	Guillain-Barré syndrome
Demyelinating diseases of the central nervous system	Subacute sclerosing panencephalitis	Aseptic meningitis	Guillain-Barré syndrome (IPV)	Demyelinating diseases of the central nervous system	Transverse myelitis
Mononeuropathy	Residual seizure disorder	Sensorineural deafness (MMR)	Death from SIDS[c]	Arthritis	Thrombocytopenia
Arthritis	Sensorineural deafness (MMR)	Insulin-dependent diabetes mellitus		Death from SIDS[c]	Anaphylaxis
	Optic neuritis	Sterility			Death from SIDS[c]
Erythema multiforme	Transverse myelitis	Thrombocytopenia			
	Guillain-Barré syndrome	Anaphylaxis[d]			
	Thrombocytopenia				
	Insulin-dependent diabetes mellitus				
Category 3: The Evidence Favors Rejection of a Causal Relation					
Encephalopathy[e]					Early onset *H. influenzae* b disease (conjugate vaccines)
Infantile spasms (DT only)[f]					
Death from SIDS (DT only)[f,g]					
Category 4: The Evidence Favors Acceptance of a Causal Relation					
Guillain-Barré syndrome[h]	Anaphylaxis[d]		Guillain-Barré syndrome (OPV)		Early-onset *H. influenzae* b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine
Brachial neuritis[i]					

APPENDIX C. IOM CONCLUSIONS, 1991

TABLE 1-2 Summary of Conclusions by Adverse Event for DPT[a] and RA 27/3 MMR[b] Vaccines

Conclusion	Adverse Events Reviewed	
	DPT Vaccine	RA 27/3 Rubella Vaccine
1. No evidence bearing on a causal relation[c]	Autism	
2. Evidence insufficient to indicate a causal relation[d]	Aseptic meningitis Chronic neurologic damage Erythema multiforme or other rash Guillain-Barré syndrome Hemolytic anemia Juvenile diabetes Learning disabilities and attention-deficit disorder Peripheral mononeuropathy Thrombocytopenia	Radiculoneuritis and other neuropathies Thrombocytopenic purpura
3. Evidence does not indicate a causal relation[e]	Infantile spasms Hypsarrythmia Reye syndrome Sudden infant death syndrome	
4. Evidence is consistent with a causal relation[f]	Acute encephalopathy[g] Shock and "unusual shock-like state"	Chronic arthritis
5. Evidence indicates a causal relation[h]	Anaphylaxis Protracted, inconsolable crying	Acute arthritis

[a]Evidence does not differentiate between DPT vaccine and the pertussis component of DPT vaccine except in the case of protracted, inconsolable crying where the evidence implicates the pertussis component specifically.

[b]RA 27/3 MMR, Trivalent measles-mumps-rubella vaccine containing the RA 27/3 rubella strain.

[c]No category of evidence was found bearing on a judgment about causation (all categories of evidence left blank in Table 1-1).

[d]Relevant evidence in one or more categories was identified but was judged to be insufficient to indicate whether or not a causal relation exists (no category of evidence checked as supporting causation in Table 1-1; exceptions are this designation under biologic plausibility for erythema multiforme and hemolytic anemia).

[e]The available evidence, on balance, does not indicate a causal relation (one or more categories of evidence checked as not supporting causation in Table 1-1, with evidence supporting causation being either absent or outweighed by the other evidence).

[f]The available evidence, on balance, tends to support a causal relation (one or more categories of evidence checked as supporting causation in Table 1-1, with evidence checked as insufficient or not supporting causation being absent or outweighed by the other evidence).

[g]Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

[h]The available evidence, on balance, supports a causal relation, and the evidence is more persuasive than that for conclusion 4 above (the categories of evidence are coded similarly to those in conclusion 4, with evidence checked as insufficient or not supporting causation in Table 1-1 being absent or less than for 4).

TABLE 1-2 *(continued)*

DT/Td/T	Measles[a]	Mumps[a]	OPV/IPV[b]	Hepatitis B	*H. influenzae* type b
Category 5: The Evidence Establishes a Causal Relation					
Anaphylaxis[h]	Thrombocytopenia (MMR)		Poliomyelitis in recipient or contact (OPV)	Anaphylaxis	
	Anaphylaxis (MMR)[d]				
	Death from measles vaccine-strain viral infection[c,i]		Death from polio vaccine-strain viral infection[c,i]		

[a]If the data derive from a monovalent preparation, then in the committee's judgment the causal relation extends to multivalent preparations. If the data derive exclusively from MMR, that is so indicated by (MMR). In the absence of any data on the monovalent preparation, in the committee's judgment the causal relation determined for the multivalent preparations does not extend to the monovalent components.

[b]For some adverse events, the committee was charged with assessing the causal relation between the adverse event and only oral polio vaccine (OPV) (paralytic and nonparalytic poliomyelitis) or only inactivated polio vaccine (IPV) (anaphylaxis and thrombocytopenia). If the conclusions are different for OPV than for IPV for the other adverse events, that is so noted.

[c]This table lists weight-of-evidence determinations only for deaths that are classified as SIDS and deaths that are a consequence of vaccine-strain viral infection. However, if the evidence favors the acceptance of (or establishes) a causal relation between a vaccine and an adverse event, and that adverse event can be fatal, then in the committee's judgment the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a vaccine-associated adverse event is limited to tetanus-diphtheria toxoid for adult use (Td) and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and OPV and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *H. influenzae* type b unconjugated PRP vaccine and early-onset *H. influenzae* type b disease in children age 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See Chapter 10 for details.

[d]The evidence that establishes a causal relation for anaphylaxis derives from MMR. The evidence regarding monovalent measles vaccine favors acceptance of a causal relation, but are less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

[e]The evidence derives from studies of diphtheria-tetanus toxoid for pediatric use (DT). If the evidence favors rejection of a causal relation between DT and encephalopathy, then in the committee's judgment the evidence favors rejection of a causal relation between Td and tetanus toxoid and encephalopathy.

[f]Infantile spasms and SIDS occur only in an age group that receives DT but not Td or tetanus toxoid.

[g]The evidence derives mostly from DPT. Because there are supportive data favoring rejection of a causal relation between DT and SIDS as well, if the evidence favors rejection of a causal relation between DPT and SIDS, then in the committee's judgment the evidence favors rejection of a causal relation between DT and SIDS.

[h]The evidence derives from tetanus toxoid. If the evidence favors acceptance of (or establishes) a causal relation between tetanus toxoid and an adverse event, then in the committee's judgment the evidence favors acceptance of (or establishes) a causal relation between DT and Td and the adverse event as well.

[i]The data come primarily from individuals proven to be immunocompromised.